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**WO 03/024450 A1**

(54) Title: METHODS FOR TREATING PRION DISEASES

(57) Abstract: The invention provides safe and effective methods for treating and preventing prion diseases by administering a therapeutically effective amount of at least one cholinesterase inhibitor. A preferred cholinesterase inhibitor is donepezil, stereoisomers thereof, or pharmaceutically acceptable salts thereof, such as ARICEPT<sup>®</sup>. Prion diseases, which are characterized by one or more symptoms of dementia and/or cognitive impairments, include, for example, Creutzfeldt-Jakob Disease, variant Creutzfeldt-Jakob Disease, Gerstmann-Sträussler-Scheinker disease, fatal familial insomnia, and kuru. In other embodiments, the invention provides methods for treating cognitive impairments due to surgery by administering a therapeutically effective amount of at least one cholinesterase inhibitor.

## **Methods for Treating Prion Diseases**

### **Related Application**

This application claims priority to US Provisional Application No. 60/323,331 filed September 20, 2001, the disclosure of which is incorporated by reference herein in  
5 its entirety.

### **Field of the Invention**

The invention provides methods for treating and preventing prion diseases in a patient in need thereof by administering an effective amount of at least one cholinesterase inhibitor. A preferred cholinesterase inhibitor is donepezil  
10 hydrochloride or ARICEPT®.

### **Background of the Invention**

Mad cow disease, also known as bovine spongiform encephalopathy (BSE), is a chronic degenerative disease affecting the central nervous system of cattle. Since 1986 mad cow disease has been diagnosed in the United Kingdom, Belgium, the Czech  
15 Republic, Denmark, France, Germany, Greece, Ireland, Italy, Luxembourg, Liechtenstein, the Netherlands, Northern Ireland, Portugal, Spain and Switzerland. Research has found a causal relationship between mad cow disease and variant Creutzfeldt-Jakob Disease in humans. Humans who eat beef infected with mad cow disease may contract variant Creutzfeldt-Jakob Disease. There is a need in the art for  
20 treatments for variant Creutzfeldt-Jakob Disease and other prion diseases. The invention is directed to this, as well as other, important ends.

### **Summary of the Invention**

The invention provides methods for treating and preventing prion diseases in humans by administering to a patient in need thereof an effective amount of at least one  
25 cholinesterase inhibitor. The cholinesterase inhibitor is preferably donepezil, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof. Prion diseases include, for example, Creutzfeldt-Jakob Disease, variant Creutzfeldt-Jakob Disease, Gerstmann-Sträussler-Scheinker disease, fatal familial insomnia, and kuru.

In another embodiment, the invention provides methods for treating and  
30 preventing cognitive impairments and/or dementia caused by surgery by administering

to a patient in need thereof an effective amount of at least one cholinesterase inhibitor.

### Detailed Description of the Invention

Prion diseases are generally inherited or transmitted from host to host of a single species or from one species to another. Prion diseases, which destroy brain tissue, are characterized by dementia.

Creutzfeldt-Jakob Disease is a brain disorder which causes a rapid, progressive dementia and associated neuromuscular disturbances. About 10-15% of the cases of Creutzfeldt-Jakob Disease are inherited, while the remaining cases are thought to be caused by abnormal prion proteins. There are some cases of Creutzfeldt-Jakob Disease, called sporadic Creutzfeldt-Jakob Disease, that have no known cause.

Variant Creutzfeldt-Jakob Disease is generally transmitted to humans by eating beef from cows having mad cow disease. Variant Creutzfeldt-Jakob Disease is a brain disorder which causes a rapid, progressive dementia and associated neuromuscular disturbances. Variant Creutzfeldt-Jakob Disease differs from Creutzfeldt-Jakob Disease in that the patients are often times younger, the course of the disease is longer, and electroencephalographic electrical activity in the brain is not typical of Creutzfeldt-Jakob Disease. *In vivo* research has shown that mice inoculated with mad cow disease showed the same pattern of incubation time, clinical signs and brains lesions as mice inoculated with tissues from patients with variant Creutzfeldt-Jakob Disease. See [www.aphis.usda.gov/oa/bse](http://www.aphis.usda.gov/oa/bse), the disclosure of which is incorporated by reference herein in its entirety.

Gerstmann-Sträussler-Scheinker disease, primarily a genetic disorder, is characterized by cerebellar ataxia, progressive dementia, and coordination/movement problems.

Fatal familial insomnia, primarily a genetic disorder, is caused by the degeneration of the thalamus, and is characterized by symptoms of sleeping problems and dementia.

Kuru is a neurodegenerative disorder found in Papua New Guinea in humans who practiced cannibalism. Kuru is characterized by progressive problems with coordination which are typically followed by dementia. Kuru has essentially been

eliminated since the cessation of the ritual handling and eating of the brains of deceased relatives.

“Dementia” refers to a global deterioration of intellectual functioning in clear consciousness, and is characterized by one or more symptoms of disorientation,  
5 impaired memory, impaired judgment, and/or impaired intellect.

“Cognitive impairment” refers to an acquired deficit in one or more of memory function, problem solving, orientation and/or abstraction that impinges on an individual’s ability to function independently.

“Cognitive impairments and/or dementia caused by surgery” refers to cognitive  
10 impairments and/or dementia that occur following a surgical procedure where the patient has been under anesthesia; has been on an artificial ventilation device; has been on an artificial blood pumping device; has had low blood pressure or blood flow; and/or has had lower than normal oxygen concentrations in the blood. The surgery can be a traumatic surgery such as, for example, organ (e.g., heart, lung, kidney) transplants;  
15 brain surgery; or surgery to remove a tumor. Without intending to be bound by any theory of the invention, surgery exposes a patient’s brain to numerous conditions (e.g., inflammation, lack of oxygen, elevated blood sugar, lowered body temperature, microscopic blood clots, amnesia-causing drugs) that may be the cause of cognitive impairments and/or dementia.

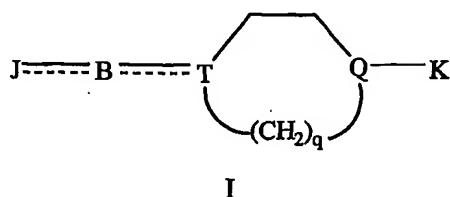
20 “Patient” refers to animals, preferably mammals, more preferably humans. The term “patient” includes adults and children, and includes men and women. Children includes neonates, infants, and adolescents.

The invention provides methods for treating and preventing prion diseases by administering to a patient in need thereof a therapeutically effective amount of at least  
25 one cholinesterase inhibitor. Preferably, the invention provides methods for treating one or more symptoms of the dementia and/or cognitive impairments that are symptomatic of (i.e., associated with or caused by) prion diseases. “Treating” refers to eliminating and/or alleviating one or more symptoms of dementia and/or cognitive impairments (e.g., compared to the symptoms prior to administering one or more  
30 cholinesterase inhibitors).

The invention also provides methods for treating and/or preventing cognitive impairments and/or dementia caused by surgery. "Treating" refers to eliminating and/or alleviating one or more symptoms of dementia and/or cognitive impairments (e.g., compared to the symptoms prior to administering one or more cholinesterase inhibitors).

The cholinesterase inhibitor can be any known in the art. Exemplary cholinesterase inhibitors include donepezil, tacrine, physostigmine, rivastigmine, galantamine, citicoline, velnacrine maleate, metrifonate, heptastigmine, and the like.

In one embodiment, the cholinesterase inhibitor is a compound of formula I, a  
10 stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof:



wherein J is

- 15 (a) a substituted or unsubstituted group selected from the group consisting of (1) phenyl, (2) pyridyl, (3) pyrazyl, (4) quinolyl, (5) cyclohexyl, (6) quinoxalyl, and (7) furyl;
- (b) a monovalent or divalent group, in which the phenyl may have one or more substituents selected from (1) indanyl, (2) indanonyl, (3) indenyl, (4) indenonyl, (5) indanedionyl, (6) tetralonyl, (7) benzosuberonyl, (8) 20 indanolyl, and (9)  $C_6H_5-CO-CH(CH_3)-$ ;
- (c) a monovalent group derived from a cyclic amide compound;
- (d) a lower alkyl group; or
- (e) a group of  $R^{21}-CH=CH-$ , in which  $R^{21}$  is hydrogen or a lower alkoxycarbonyl group;

25 B is  $-(\text{CHR}^{22})_{\text{r}}, -\text{CO}-(\text{CHR}^{22})_{\text{r}}, -\text{NR}^4-(\text{CHR}^{22})_{\text{r}}, -\text{CO}-\text{NR}^5-(\text{CHR}^{22})_{\text{r}},$   
 $-\text{CH}=\text{CH}-(\text{CHR}^{22})_{\text{r}}, -\text{OCOO}-(\text{CHR}^{22})_{\text{r}}, -\text{OOC}-\text{NH}-(\text{CHR}^{22})_{\text{r}}, -\text{NH}-\text{CO}-(\text{CHR}^{22})_{\text{r}},$   
 $-\text{CH}_2-\text{CO}-\text{NH}-(\text{CHR}^{22})_{\text{r}}, -(\text{CH}_2)_2-\text{NH}-(\text{CHR}^{22})_{\text{r}}, -\text{CH}(\text{OH})-(\text{CHR}^{22})_{\text{r}},$   
 $=(\text{CH}-\text{CH}=\text{CH})_{\text{b}}, =\text{CH}-(\text{CH}_2)_{\text{c}}, =(\text{CH}-\text{CH})_{\text{d}}, -\text{CO}-\text{CH}=\text{CH}-\text{CH}_2-$

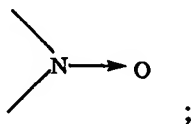
-CO-CH<sub>2</sub>-CH(OH)-CH<sub>2</sub>-, -CH(CH<sub>3</sub>)-CO-NH-CH<sub>2</sub>-, -CH=CH-CO-NH-(CH<sub>2</sub>)<sub>2</sub>-, -NH-,  
-O-, -S-, a dialkylaminoalkyl-carbonyl or a lower alkoxy carbonyl;

wherein R<sup>4</sup> is hydrogen, lower alkyl, acyl, lower alkylsulfonyl, phenyl,  
substituted phenyl, benzyl, or substituted benzyl; R<sup>5</sup> is hydrogen, lower alkyl or phenyl;

- 5 r is zero or an integer of about 1 to about 10; R<sup>22</sup> is hydrogen or methyl so that one  
alkylene group may have no methyl branch or one or more methyl branches; b is an  
integer of about 1 to about 3; c is zero or an integer of about 1 to about 9; d is zero or  
an integer of about 1 to about 5;

T is nitrogen or carbon;

- 10 Q is nitrogen, carbon or

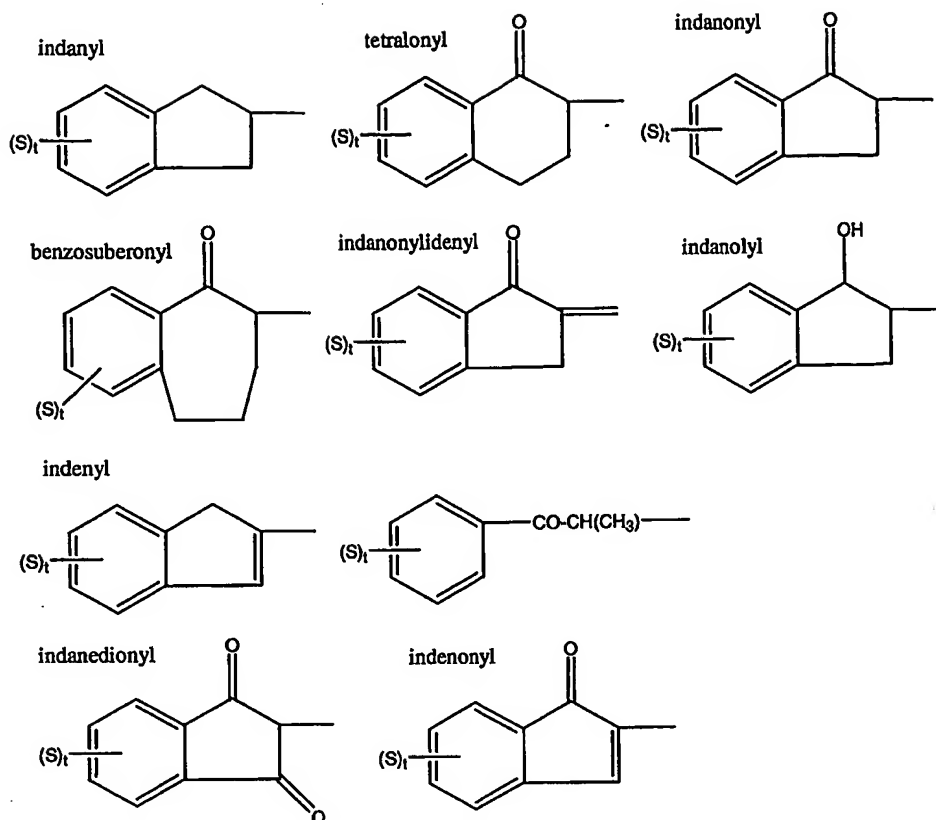


q is an integer of about 1 to about 3;

- K is hydrogen, phenyl, substituted phenyl, arylalkyl in which the phenyl may  
have a substituent, cinnamyl, a lower alkyl, pyridylmethyl, cycloalkylalkyl,  
15 adamantanemethyl, furylmenthyl, cycloalkyl, lower alkoxy carbonyl or an acyl; and

----- is a single bond or a double bond.

- In the compound of formula I, J is preferably (a) or (b), more preferably (b). In  
the definition of (b), a monovalent group (2), (3) and (5) and a divalent group (2) are  
preferred. The group (b) preferably includes, for example, the groups having the  
20 formulae shown below:



wherein  $t$  is an integer of about 1 to about 4; and each  $S$  is independently hydrogen or a substituent, such as a lower alkyl having 1 to 6 carbon atoms or a lower alkoxy having 1 to 6 carbon atoms. Among the substituents, methoxy is most preferred. The phenyl is most preferred to have 1 to 3 methoxy groups thereon.  $(S)_t$  may form methylene dioxy groups or ethylene dioxy groups on two adjacent carbon atoms of the phenyl group. Of the above groups, indanonyl, indanedionyl and indenyl, optionally having substituents on the phenyl, are the most preferred.

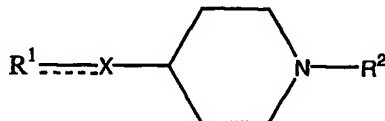
In the definition of  $B$ ,  $-(CHR^{22})_r$ ,  $-\text{CO}-(CHR^{22})_r$ ,  $=(\text{CH}-\text{CH}=\text{CH})_b$ ,  $=\text{CH}-(\text{CH}_2)_c$  and  $=(\text{CH}-\text{CH})_d$  are preferable. The group of  $-(CHR^{22})_r$  in which  $R^{22}$  is hydrogen and  $r$  is an integer of 1 to 3, and the group of  $=\text{CH}-(\text{CH}_2)_c$  are most preferable. The preferable groups of  $B$  can be connected with (b) of  $J$ , in particular (b)(2).

The ring containing  $T$  and  $Q$  in formula I can be 5-, 6- or 7-membered. It is preferred that  $Q$  is nitrogen,  $T$  is carbon or nitrogen, and  $q$  is 2; or that  $Q$  is nitrogen,  $T$

is carbon, and q is 1 or 3; or that Q is carbon, T is nitrogen and q is 2.

It is preferable that K is a phenyl, arylalkyl, cinnamyl, phenylalkyl or a phenylalkyl having a substituent(s) on the phenyl.

In preferred embodiments, the cyclic amine compounds of formula I are the  
 5 piperidine compounds of formula II, a stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof:



II

wherein R<sup>1</sup> is a (1) substituted or unsubstituted phenyl group; (2) a substituted  
 10 or unsubstituted pyridyl group; (3) a substituted or unsubstituted pyrazyl group; (4) a substituted or unsubstituted quinolyl group; (5) a substituted or unsubstituted indanyl group; (6) a substituted or unsubstituted cyclohexyl group; (7) a substituted or unsubstituted quinoxalyl group; (8) a substituted or unsubstituted furyl group; (9) a monovalent or divalent group derived from an indanone having a substituted or  
 15 unsubstituted phenyl ring; (10) a monovalent group derived from a cyclic amide compound; (11) a lower alkyl group; or (12) a group of the formula R<sup>3</sup>-CH=C-, where R<sup>3</sup> is a hydrogen atom or a lower alkoxy carbonyl group;

X is -(CH<sub>2</sub>)<sub>n</sub>-, -C(O)-(CH<sub>2</sub>)<sub>n</sub>-, -N(R<sup>4</sup>)-(CH<sub>2</sub>)<sub>n</sub>-, -C(O)-N(R<sup>5</sup>)-(CH<sub>2</sub>)<sub>n</sub>-,  
 -CH=CH-(CH<sub>2</sub>)<sub>n</sub>-, -O-C(O)-O-(CH<sub>2</sub>)<sub>n</sub>-, -O-C(O)-NH-(CH<sub>2</sub>)<sub>n</sub>-, -CH=CH-CH=CO-,  
 20 -NH-C(O)-(CH<sub>2</sub>)<sub>n</sub>-, -CH<sub>2</sub>-C(O)-NH-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>2</sub>-C(O)-NH-(CH<sub>2</sub>)<sub>n</sub>-,  
 -CH(OH)-(CH<sub>2</sub>)<sub>n</sub>-, -C(O)-CH=CH-CH<sub>2</sub>-, -C(O)-CH<sub>2</sub>-CH(OH)-CH<sub>2</sub>-,  
 -CH(CH<sub>3</sub>)-C(O)-NH-CH<sub>2</sub>-, -CH=CH-C(O)-NH-(CH<sub>2</sub>)<sub>2</sub>-, a dialkylaminoalkylcarbonyl group, a lower alkoxy carbonyl group;

where n is an integer of 0 to 6; R<sup>4</sup> is a hydrogen atom, a lower alkyl group, an  
 25 acyl group, a lower alkylsulfonyl group, a substituted or unsubstituted phenyl group, or a substituted or unsubstituted benzyl group; and R<sup>5</sup> is a hydrogen atom a lower alkyl group or a phenyl group;

R<sup>2</sup> is a substituted or unsubstituted phenyl group; a substituted or unsubstituted



arylalkyl group; a cinnamyl group; a lower alkyl group; a pyridylmethyl group; a cycloalkylalkyl group; an adamantanemethyl group; or a furoylmethyl group; and

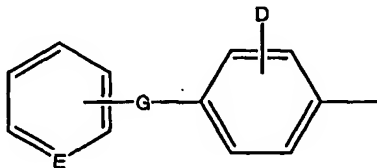
----- is a single bond or a double bond.

The term "lower alkyl group" as used herein means a straight or branched alkyl group having 1 to 6 carbon atoms. Exemplary "lower alkyl groups" include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl (amyl), isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1-methylpentyl, 2-methyl-pentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethyl-butyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, and the like. The lower alkyl group is preferably methyl, ethyl, propyl or isopropyl; more preferably methyl.

Specific examples of the substituents for the substituted or unsubstituted phenyl, pyridyl, pyrazyl, quinolyl, indanyl, cyclohexyl, quinoxalyl and furyl groups in the definition of R<sup>1</sup> include lower alkyl groups having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, and tert-butyl groups; lower alkoxy groups corresponding to the above-described lower alkyl groups, such as methoxy and ethoxy groups; a nitro group; halogen atoms, such as chlorine, fluorine and bromine; a carboxyl group; lower alkoxycarbonyl groups corresponding to the above-described lower alkoxy groups, such as methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, n-propoxycarbonyl, and n-butyloxycarbonyl groups; an amino group; a lower monoalkylamino group; a lower dialkylamino group; a carbamoyl group; acylamino groups derived from aliphatic saturated monocarboxylic acids having 1 to 6 carbon atoms, such as acetylamino, propionylamino, butyrylamino, isobutyrylamino, valerylamino, and pivaloylamino groups; cycloalkyloxycarbonyl groups, such as a cyclohexyloxycarbonyl group; lower alkylaminocarbonyl groups, such as methylaminocarbonyl and ethylaminocarbonyl groups; lower alkylcarbonyloxy groups corresponding to the above-defined lower alkyl groups, such as methylcarbonyloxy, ethylcarbonyloxy, and n-propylcarbonyloxy groups; halogenated lower alkyl groups, such as a trifluoromethyl group; a hydroxyl group; a formyl group; and lower alkoxy

lower alkyl groups, such as ethoxymethyl, methoxymethyl and methoxyethyl groups. The "lower alkyl groups" and "lower alkoxy groups" in the above description of the substituent include all the groups derived from the above-mentioned groups. The substituent may be one to three of them, which may be the same or different.

- 5           When the substituent is a phenyl group, the following group is within the scope of the substituted phenyl group:



wherein G is -C(O)-, -O-C(O)-, -O-, -CH<sub>2</sub>-NH-C(O)-, -CH<sub>2</sub>-O-, -CH<sub>2</sub>-SO<sub>2</sub>-, -CH(OH)-, or -CH<sub>2</sub>-S(→O)-; E is a carbon or nitrogen atom; and D is a substituent.

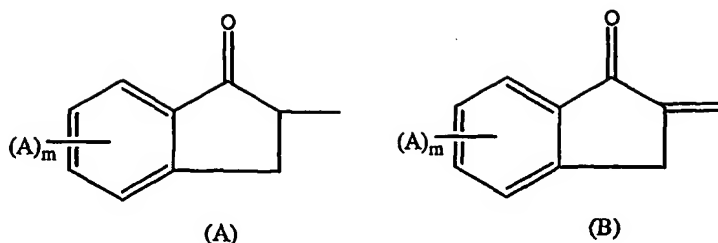
- 10           Preferred examples of the substituents (i.e., "D") for the phenyl group include lower alkyl, lower alkoxy, nitro, halogenated lower alkyl, lower alkoxy carbonyl, formyl, hydroxyl, and lower alkoxy lower alkyl groups, halogen atoms, and benzyl and benzyldisulfonyl groups. The substituent may be two or more of them, which may be the same or different.

- 15           Preferred examples of the substituent for the pyridyl group include lower alkyl and amino groups and halogen atoms.

Preferred examples of the substituent for the pyrazyl group include lower alkoxy carbonyl, carboxyl, acylamino, carbamoyl, and cycloalkyloxy carbonyl groups.

- 20           With respect to R<sup>1</sup>, the pyridyl group is preferably a 2-pyridyl, 3-pyridyl, or 4-pyridyl group; the pyrazyl group is preferably a 2-pyrazinyl group; the quinolyl group is preferably a 2-quinolyl or 3-quinolyl group; the quinoxaliny group is preferably a 2-quinoxaliny or 3-quinoxaliny group; and the furyl group is preferably a 2-furyl group.

- 25           Specific examples of preferred monovalent or divalent groups derived from an indanone having an unsubstituted or substituted phenyl ring include those represented by formulas (A) and (B):



where  $m$  is an integer of from 1 to 4, and each  $A$  is independently a hydrogen atom, a lower alkyl group, a lower alkoxy group, a nitro group, a halogen atom, a carboxyl group, a lower alkoxycarbonyl group, an amino group, a lower

5 monoalkylamino group, a lower dialkylamino group, a carbamoyl group, an acylamino group derived from aliphatic saturated monocarboxylic acids having 1 to 6 carbon atoms, a cycloalkyloxycarbonyl group, a lower alkylaminocarbonyl group, a lower alkylcarbonyloxy group, a halogenated lower alkyl group, a hydroxyl group, a formyl group, or a lower alkoxy lower alkyl group; preferably a hydrogen atom, a lower alkyl

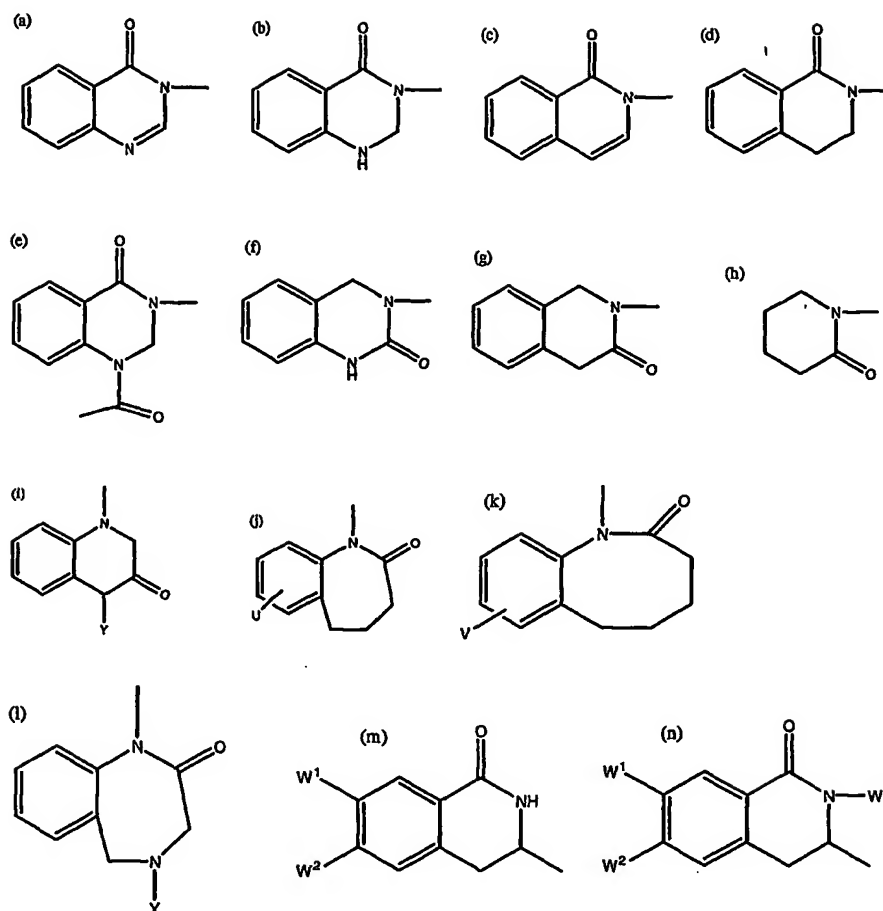
10 group or a lower alkoxy group; most preferably the indanone group is unsubstituted or substituted with 1 to 3 methoxy groups.

Examples of the monovalent group derived from a cyclic amide compound include quinazolone, tetrahydroisoquinolinone, tetrahydrobenzodiazepinone, and hexahydrobenzazocinone. However, the monovalent group may be any one having a

15 cyclic amide group in the structural formula thereof, and is not limited to the above-described specific examples. The cyclic amide group may be one derived from a monocyclic or condensed heterocyclic ring. The condensed heterocyclic ring is preferably one formed by condensation with a phenyl ring. In this case, the phenyl ring may be substituted with a lower alkyl group having 1 to 6 carbon atoms, preferably a

20 methyl group, or a lower alkoxy group having 1 to 6 carbon atoms, preferably a methoxy group.

Preferred examples of the monovalent group include the following:



In the above formulae, Y is a hydrogen atom or a lower alkyl group; V and U are each a hydrogen atom or a lower alkoxy group (preferably dimethoxy); W<sup>1</sup> and W<sup>2</sup> are each a hydrogen atom, a lower alkyl group, or a lower alkoxy group; and W<sup>3</sup> is a hydrogen atom or a lower alkyl group. The right hand ring in formulae (j) and (l) is a 7-membered ring, while the right hand ring in formula (k) is an 8-membered ring.

The most preferred examples of the above-defined R<sup>1</sup> include a monovalent group derived from an indanone having an unsubstituted or substituted phenyl group and a monovalent group derived from a cyclic amide compound.

The most preferred examples of the above-defined X include  $-(CH_2)_n-$ , an amide group, or groups represented by the above formulae where n is 2. Thus, it is most preferred that any portion of a group represented by the formula  $R^1-----X---$  have a carbonyl or amide group.

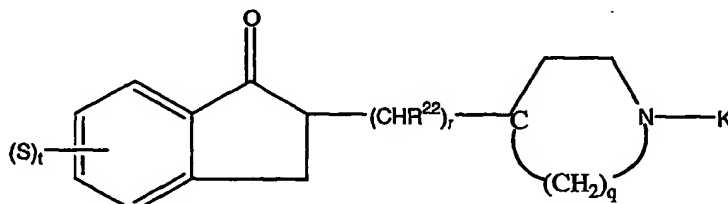
The substituents involved in the expressions "a substituted or unsubstituted phenyl group" and "a substituted or unsubstituted arylalkyl group" in the above definition of  $R^2$  are the same substituents as those described for the above definitions of a phenyl group, a pyridyl group, a pyrazyl group, a quinolyl group, an indanyl group, a  
 5 cyclohexyl group, a quinoxalyl group or a furyl group in the definition of  $R^1$ .

The term "arylalkyl group" is intended to mean an unsubstituted benzyl or phenethyl group or the like.

Specific examples of the pyridylmethyl group include 2-pyridylmethyl, 3-pyridylmethyl, and 4-pyridylmethyl groups.

10 Preferred examples of  $R^2$  include benzyl and phenethyl groups. The symbol  $\text{---}\text{---}\text{---}$  means a double or single bond. The bond is a double bond only when  $R^1$  is the divalent group (B) derived from an indanone having an unsubstituted or substituted phenyl ring, while it is a single bond in other cases.

In preferred embodiments, the compound of formula II is a compound of  
 15 formula III, a stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof:



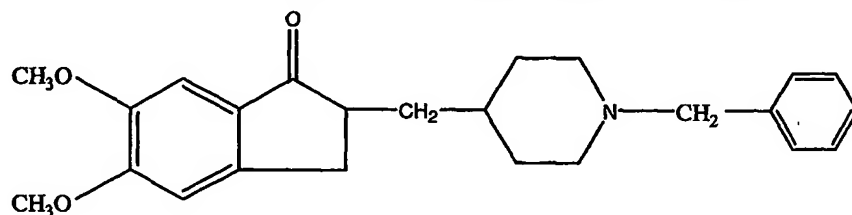
III

wherein  $r$  is an integer of about 1 to about 10; each  $R^{22}$  is independently hydrogen or methyl;  $K$  is a phenalkyl or a phenalkyl having a substituent on the phenyl  
 20 ring; each  $S$  is independently a hydrogen, a lower alkyl group having 1 to 6 carbon atoms or a lower alkoxy group having 1 to 6 carbon atoms;  $t$  is an integer of 1 to 4;  $q$  is an integer of about 1 to about 3; with the proviso that  $(S)_t$  can be a methylenedioxy group or an ethylenedioxy group joined to two adjacent carbon atoms of the phenyl ring.

25 In preferred embodiments, the compound of formula III is 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-dimethoxy-1-indanon)-

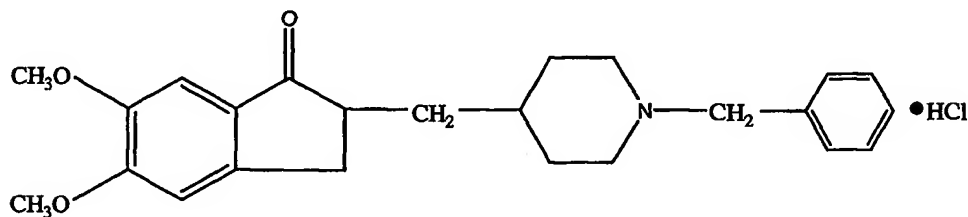
2-ylidenyl)-methylpiperidine; 1-benzyl-4-((5-methoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-diethoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-methylenedioxy-1-indanon)-2-yl)methylpiperidine; 1-(m-nitrobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-cyclohexylmethyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-(m-fluorobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)propylpiperidine; 1-benzyl-4-((5-isopropoxy-6-methoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-dimethoxy-1-oxoindanon)-2-yl)propenylpiperidine; or pharmaceutically acceptable salts thereof.

10 In more preferred embodiments, the compound of formula III is 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine, a stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof, which is represented by formula IV:



IV.

15 In the most preferred embodiment, the compound of formula III is 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine hydrochloride or a stereoisomer thereof, which is also known as donepezil hydrochloride or ARICEPT® (Eisai Inc., Teaneck, NJ), and which has formula IVa:



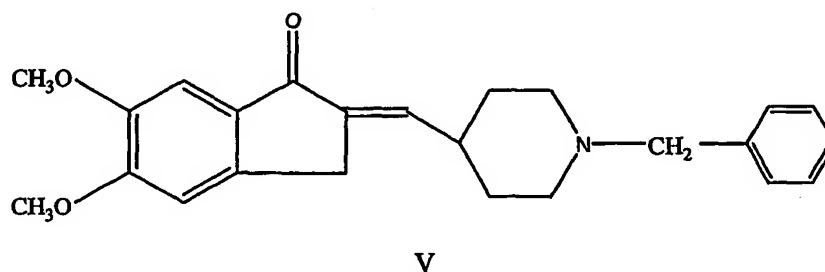
IVa.

20 The compounds of the invention may have an asymmetric carbon atom(s), depending upon the substituents, and can have stereoisomers, which are within the

scope of the invention. For example, donepezil hydrochloride can be in the forms described in Japanese Patent Application Nos. 4-187674 and 4-21670, the disclosures of which are incorporated by reference herein in their entirety.

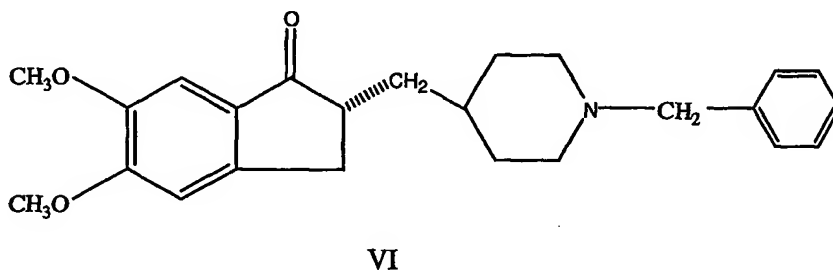
Japanese Patent Application No. 4-187674 describes a compound having

5 formula V:

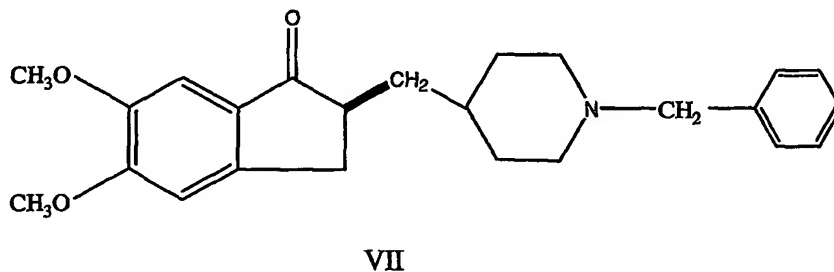


which can be in the form of a pharmaceutically acceptable salt, such as a hydrochloride salt. Japanese Patent Application No. 4-21670 describes compounds having formula

10 VI:

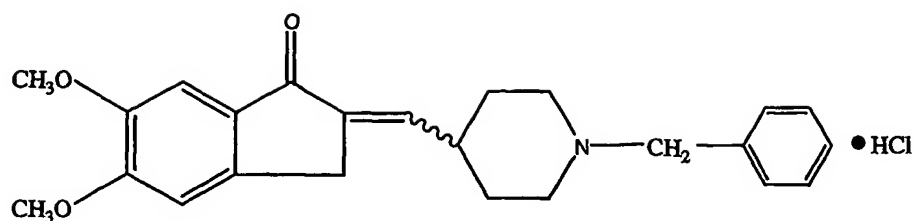


which can be in the form of a pharmaceutically acceptable salt, such as a hydrochloride salt; and compounds of formula VII:



15

which can be in the form of a pharmaceutically acceptable salt, such as a hydrochloride salt; and compounds of formula VIII:



VIII.

The compounds of the invention can be administered in the form of a pharmaceutically acceptable salt. Pharmaceutically acceptable salts are known in the art and include those of inorganic acids, such as hydrochloride, sulfate, hydrobromide and phosphate; and those of organic acids, such as formate, acetate, trifluoroacetate, methanesulfonate, benzenesulfonate and toluenesulfonate. When certain substituents are selected, the compounds of the present invention may form, for example, alkali metal salts, such as sodium or potassium salts; alkaline earth metal salts, such as calcium or magnesium salts; organic amine salts, such as a salt with trimethyl-amine, triethylamine, pyridine, picoline, dicyclohexylamine or N,N'-dibenzylethylenediamine. One skilled in the art will recognize that the compounds of the invention can be made in the form of any other pharmaceutically acceptable salt.

The compounds of the invention may be prepared by processes known in the art and described, for example, in U.S. Patent No. 4,895,841, WO 98/39000, and Japanese Patent Application Nos. 4-187674 and 4-21670, the disclosures of each of which are incorporated by reference herein in their entirety. Donepezil hydrochloride, a preferred cholinesterase inhibitor for use in the methods described herein, is commercially available as ARICEPT® from Eisai Inc., Teaneck, NJ.

The dosage regimen for treating or preventing the cognitive impairments and/or dementia described herein with the cholinesterase inhibitors described herein is selected in accordance with a variety of factors, including the age, weight, sex, and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular cholinesterase inhibitor used, whether a drug delivery system is used and whether the cholinesterase inhibitor is administered as part



of a drug combination.

In preferred embodiments, the cholinesterase inhibitors of the invention are administered to treat or prevent prion diseases in doses of about 0.1 milligram to about 300 milligrams per day, preferably about 1 milligram to about 100 milligrams per day, more preferably about 5 milligrams to about 10 milligrams per day. The doses can be administered in one to four portions over the course of a day, preferably once a day. One skilled in the art will recognize that when the cholinesterase inhibitors of the invention are administered to children, the dose may be smaller than the dose administered to adults, and that the dose can be dependent upon the size and weight of the patient. In preferred embodiments, a child can be administered the cholinesterase inhibitors of the invention in doses of about 0.5 milligrams to about 10 milligrams per day, preferably about 1 milligram to about 3 milligrams per day.

In preferred embodiments, a physician can administer patients donepezil hydrochloride, which is commercially available as ARICEPT® (Eisai Inc., Teaneck, NJ), as film-coated tablets containing 5 milligrams donepezil hydrochloride or 10 milligrams donepezil hydrochloride. The tablets can be administered one to about four times a day. In preferred embodiments, one 5 milligram or one 10 milligram ARICEPT® tablet is administered once a day for the methods described herein. One skilled in the art will appreciate that when donepezil hydrochloride is administered to children, the dose may be smaller than the dose that is administered to adults. In preferred embodiments, a child can be administered donepezil hydrochloride in doses of about 0.5 milligrams to about 10 milligrams per day, preferably about 1 milligram to about 3 milligrams per day.

The cholinesterase inhibitors of the invention can be administered orally, topically, parenterally, by inhalation (nasal or oral), or rectally in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intrasternal injection, or infusion techniques. Preferably, the cholinesterase inhibitors of the invention are orally administered as tablets. When administered to children, the cholinesterase inhibitors of the invention

are preferably orally administered in a liquid dosage form.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents, suspending agents (e.g., methylcellulose, Polysorbate 80, hydroxyethylcellulose, acacia, powdered tragacanth, sodium carboxymethylcellulose, polyoxyethylene sorbitan monolaurate and the like), pH modifiers, buffers, solubilizing agents (e.g., polyoxyethylene hydrogenated castor oil, Polysorbate 80, nicotinamide, polyoxyethylene sorbitan monolaurate, Macrogol, an ethyl ester of castor oil fatty acid, and the like) and preservatives. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be used are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally used as a solvent or suspending medium. For this purpose any bland fixed oil may be used including synthetic mono- or diglycerides. In addition, fatty acids, such as oleic acid, can be used to prepare injectables. The preparations can be lyophilized by methods known in the art.

Solid dosage forms for oral administration may include chewing gum, capsules, tablets, sublingual tablets, powders, granules and gels; preferably tablets. In such solid dosage forms, the active compound may be admixed with one or more inert diluents such as lactose or starch. As is normal practice, such dosage forms may also comprise other substances including lubricating agents, such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. The tablets can be prepared with enteric or film coatings, preferably film coatings.

In addition to the active ingredient, the tablets preferably comprise lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, and magnesium stearate; while the film-coating on the tablet preferably comprises talc, polyethylene glycol, hydroxypropyl methylcellulose, titanium dioxide, and, optionally, other coloring agents, such as yellow iron oxide.

Liquid dosage forms for oral administration can include pharmaceutically

acceptable emulsions, solutions, suspensions, and syrups containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

5 For administration by inhalation, the cholinesterase inhibitors of the invention can be delivered from an insufflator, a nebulizer or a pressured pack or other convenient mode of delivering an aerosol spray. Pressurized packs can include a suitable propellant. Alternatively, for administration by inhalation, the cholinesterase inhibitors can be administered in the form of a dry powder or in the form of a liquid  
10 spray.

Suppositories for rectal administration can be prepared by mixing the active compounds with suitable nonirritating excipients such as cocoa butter and polyethylene glycols that are solid at room temperature and liquid at body temperature.

For topical administration to the epidermis, the cholinesterase inhibitors of the  
15 invention can be formulated as ointments, creams or lotions, or as the active ingredient of a transdermal patch. The cholinesterase inhibitors can also be administered via iontophoresis. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and can also generally contain one or more  
20 emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, and/or coloring agents. As creams or lotions, the cholinesterase inhibitors may be mixed to form a smooth, homogeneous cream or lotion with, for example, one or more of a preservative (e.g., benzyl alcohol 1% or 2% (wt/wt)), emulsifying wax, glycerin, isopropyl palmitate, lactic acid, purified water, sorbitol solution. Such  
25 topically administrable compositions may contain polyethylene glycol 400. To form ointments, the cholinesterase inhibitors may be mixed with one or more of a preservative (e.g., benzyl alcohol 2% (wt/wt)), petrolatum, emulsifying wax, and Tenox (II) (e.g., butylated hydroxyanisole, propyl gallate, citric acid, propylene glycol). Woven pads or rolls of bandaging material, e.g., gauze, may be impregnated with the  
30 transdermally administrable compositions for topical application.

The cholinesterase inhibitors may also be topically applied using a transdermal system, such as one of an acrylic-based polymer adhesive with a resinous crosslinking agent impregnated with the cholinesterase inhibitors and laminated to an impermeable backing. For example, the cholinesterase inhibitors may be administered in the form of a transdermal patch, such as a sustained-release transdermal patch. Transdermal patches may include any conventional form such as, for example, an adhesive matrix, a polymeric matrix, a reservoir patch, a matrix- or monolithic-type laminated structure, and are generally comprised of one or more backing layers, adhesives, penetration enhancers, and/or rate-controlling membranes. Transdermal patches generally have a release liner which is removed to expose the adhesive/active ingredient(s) prior to application. Transdermal patches are described in, for example, U.S. Patent Nos. 5,262,165, 5,948,433, 6,010,715 and 6,071,531, the disclosures of which are incorporated by reference herein in their entirety.

While the cholinesterase inhibitors of the invention can be administered as the sole active pharmaceutical agent in the methods described herein, they can also be used in combination with one or more compounds which are known to be therapeutically effective against prion diseases. Known agents for treating prion diseases, such as Creutzfeldt-Jakob Disease, include mepacrine (preferably the hydrochloride salt thereof), chlorpromazine, or pharmaceutically acceptable salts thereof.

In other embodiments, the invention provides compositions comprising at least one cholinesterase inhibitor (preferably donepezil, a stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof) and at least one anti-prion disease drug, such as mepacrine, chlorpromazine and/or pharmaceutically acceptable salts thereof. The compositions preferably comprise a pharmaceutically acceptable carrier.

The invention provides combinations comprising at least one cholinesterase inhibitor, such as those described herein, and at least one anti-prion disease drug, such as those described herein, wherein the at least one cholinesterase inhibitor and at least one anti-prion disease drug are separate pharmaceutical formulations that are administered as part of the same treatment regimen, i.e., combination therapy. In preferred embodiments, the cholinesterase inhibitor is donepezil, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof. The combination is preferably

synergistic.

When administered separately, the cholinesterase inhibitors and the anti-prion disease drug can be administered about the same time as part of an overall treatment regimen, i.e., as a combination therapy. "About the same time" includes administering the cholinesterase inhibitors and anti-prion disease drugs at the same time, at different times on the same day, or on different days, as long as they are administered as part of an overall treatment regimen.

In still other embodiments, the invention provides pharmaceutical kits comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compounds and/or compositions of the invention, including, one or more cholinesterase inhibitors (e.g., donepezil, stereoisomers thereof and/or pharmaceutically acceptable salts thereof), mepacrine or a pharmaceutically acceptable salt thereof, and/or chlorpromazine or a pharmaceutically acceptable salt thereof. The cholinesterase inhibitors, mepacrine, and/or chlorpromazine may be separate components in the kit or may be in the form of a composition in the kit. The kits may also include, for example, other compounds and/or compositions, a device(s) for administering the compounds and/or compositions, and written instructions in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals.

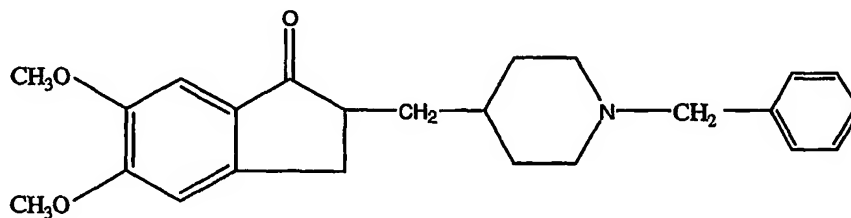
Each of the patents and publications cited herein are incorporated by reference herein in their entirety.

It will be apparent to one skilled in the art that various modifications can be made to the invention without departing from the spirit or scope of the appended claims.

## Claims

What is claimed is:

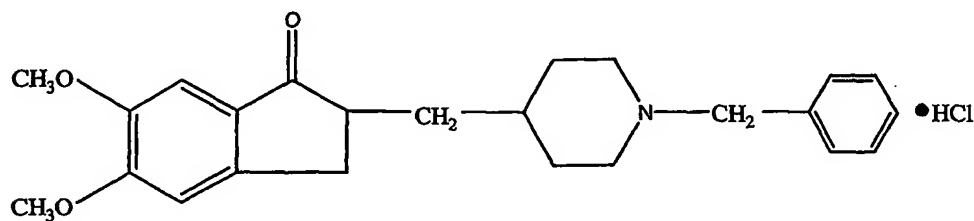
1. A method of treating a prion disease in a human in need thereof comprising administering a therapeutically effective amount of a compound of formula IV or a pharmaceutically acceptable salt thereof:



(IV)

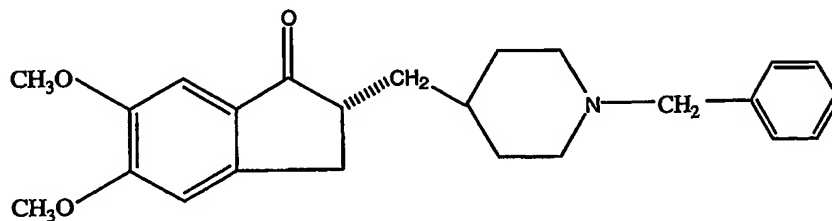
or a stereoisomer thereof.

2. The method of claim 1, wherein the method of treating the prion disease is a method of treating the dementia that is symptomatic of the prion disease.
3. The method of claim 1, wherein the prion disease is variant Creutzfeldt-Jakob Disease.
4. The method of claim 1, wherein the prion disease is Creutzfeldt-Jakob Disease.
5. The method of claim 1, wherein the prion disease is Gerstmann-Sträussler-Scheinker disease.
6. The method of claim 1, wherein the prion disease is fatal familial insomnia.
7. The method of claim 1, wherein the compound of formula IV is



or a stereoisomer thereof.

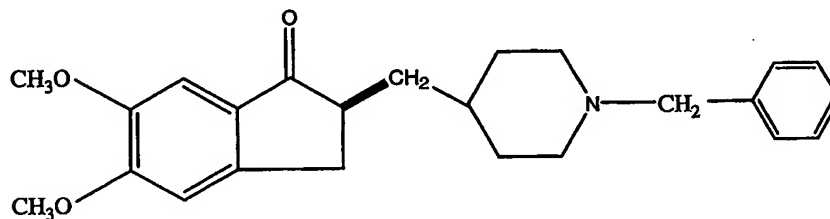
8. The method of claim 1, wherein the compound of formula IV is a compound of formula VI or a pharmaceutically acceptable salt thereof:



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(VI).

9. The method of claim 1, wherein the compound of formula IV is a compound of formula VII or a pharmaceutically acceptable salt thereof:



(VII).

10. The method of claim 1, wherein the compound of formula IV is administered in an amount of about 1 mg to about 100 mg.

11. The method of claim 10, wherein the compound of formula IV is administered in an amount of about 5 mg to about 10 mg.

12. The method of claim 1, wherein the compound of formula IV is administered in an amount of about 5 milligrams.

13. The method of claim 1, wherein the compound of formula IV is administered in an amount of about 10 milligrams.

14. The method of claim 1, wherein the compound of formula IV is orally administered.

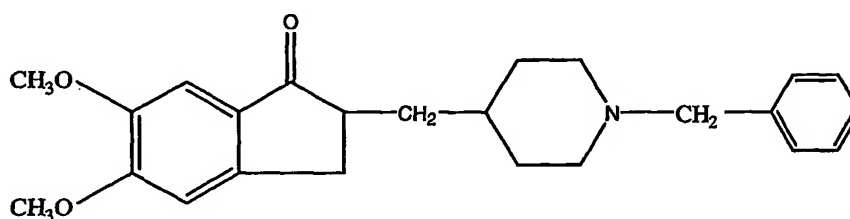
15. The method of claim 14, wherein the compound of formula IV is orally

administered in the form of a tablet.

16. The method of claim 1, further comprising administering a pharmaceutically acceptable carrier.

17. The method of claim 1, further comprising administering a therapeutically effective amount of mepacrine or a pharmaceutically acceptable salt thereof, and/or chlorpromazine or a pharmaceutically acceptable salt thereof.

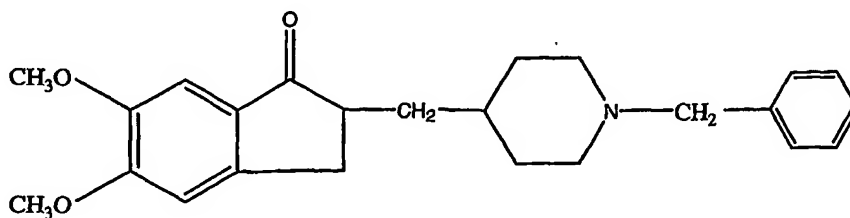
18. A composition comprising a therapeutically effective amount of at least one compound selected from mepacrine or a pharmaceutically acceptable salt thereof, and chlorpromazine or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a compound of formula IV or a pharmaceutically acceptable salt thereof:



(IV)

or a stereoisomer thereof.

19. A combination comprising a therapeutically effective amount of at least one compound selected from mepacrine or a pharmaceutically acceptable salt thereof, and chlorpromazine or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a compound of formula IV or a pharmaceutically acceptable salt thereof:

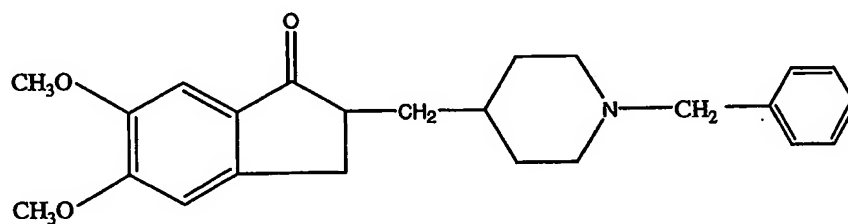


(IV)



or a stereoisomer thereof.

20. A kit comprising a therapeutically effective amount of at least one compound selected from mepacrine or a pharmaceutically acceptable salt thereof, and chlorpromazine or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a compound of formula IV or a pharmaceutically acceptable salt thereof:



(IV)

or a stereoisomer thereof.

10

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/29736

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/445

US CL : 514/319

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/319

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,895,841 A (SUGIMOTO et al.) 23 January 1990 (23.01.90), see the entire document.	1-20
A	US 6,037,361 A (ROTH et al.) 14 March 2000 (14.03.2000), see the entire document.	1-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 14 November 2002 (14.11.2002)	Date of mailing of the international search report 23 JAN 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Raymond J. Henley III Telephone No. 703-308-1235